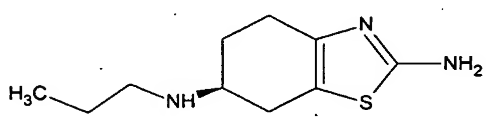
10/588564
IAP11 Rec'd PCT/PTO 04 AUG 2006

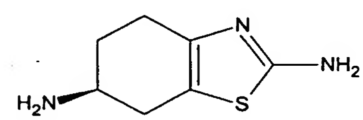
IMPROVED PROCESS FOR THE PREPARATION OF BIOLOGICALLY ACTIVE TETRAHYDROBENZTHIAZOLE DERIVATIVE

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of (S)-(-)-2-Amino-6-(n-propylamino)-4,5,6,7-tetrahydrobenzothiazole of formula (I) and its pharmaceutically acceptable salts or solvates and (S)- 2,6-diamino-4,5,6,7-tetrahydro benzothiazole an intermediate compound of formula II for formation of Pramipexole of Formula (I) . The compound of formula I is commonly known as Pramipexole which is used in the chemotherapy of Parkinson's disease and schizophrenia .More particularly, the present invention is pertaining to an improved process for the preparation of Pramipexole dihydrochloride



(I)

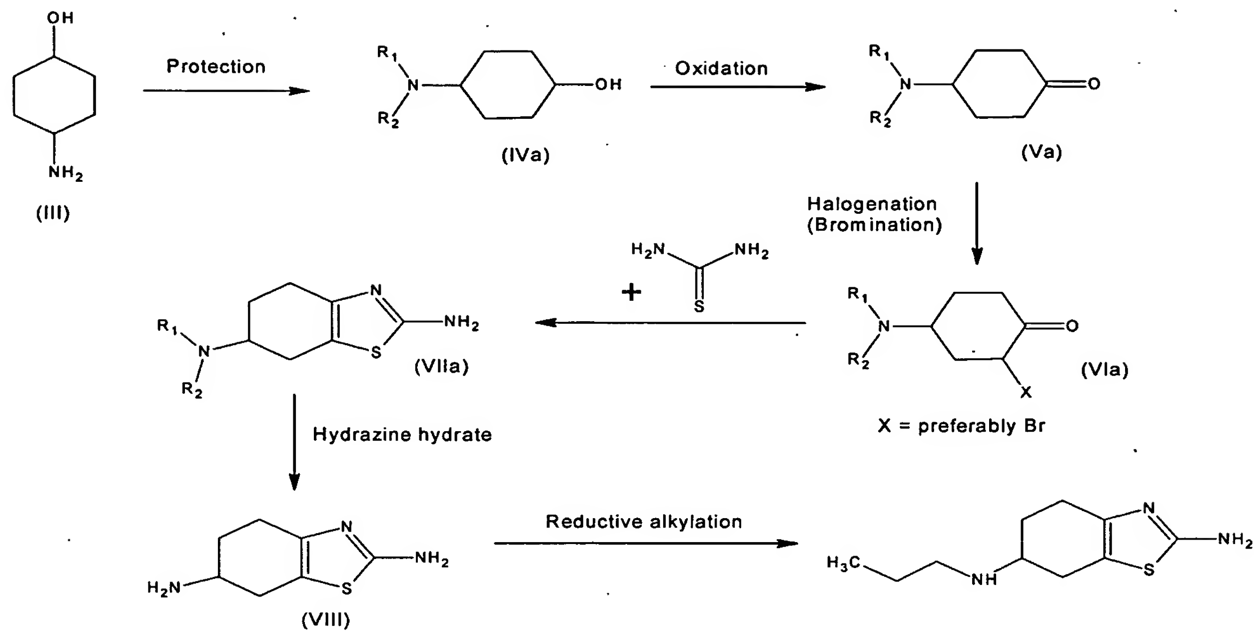


(II)

BACKGROUND AND PRIOR ART

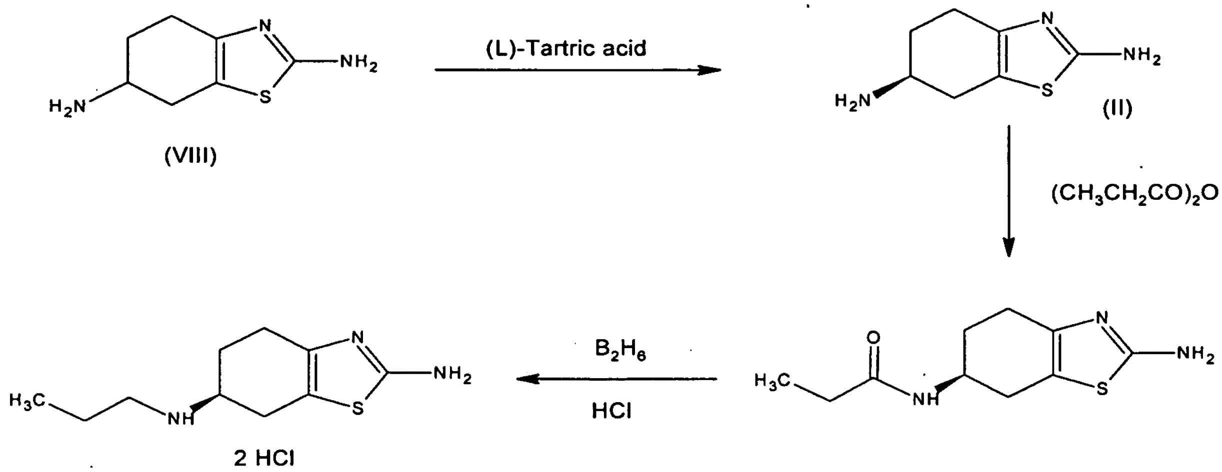
A general process for the preparation of compounds of formula (I) and (II) has been described in US 4886812, EP 186087 and EP 207696 . The process comprises the protection of amino function of 4-aminocyclohexanol (III) to give the compound of formula (IVa) wherein, R_1 is acyl or alkoxycarbonyl and R_2 is hydrogen or R_1 and R_2 together form an amino protective group such as pthalimido group which on oxidation with an oxidising agent, followed by halogenation (preferably bromination) of protected ketone of formula (Va) to give alpha halogenatedketone (VIa) which on reaction with thiourea, followed by deprotection yielded the racemic 2,6-diaminotetrahydrobenzothiole (VIIIa). Reductive alkylation of (VIIIa) with n-propanal furnished the racemic pramipexole . Although, the (S) isomer of pramipexole is mentioned therein, it is not clear at what stage the chiral resolution i.e. stage (VIII) or at final stage has been carried out. The general process steps are indicated in Scheme-1 below.

SCHEME - 1



Another process for preparing optically pure pramipexole dihydrochloride was disclosed in *J. Med. Chem.*1987, **30**,494-498 , where in, racemic 2,6-diamino-4,5,6,7-tetrahydro benzothiazole was resolved, using L (+) tartaric acid to give optically pure (S)- 2,6-diamino-4,5,6,7-tetrahydro benzothiazole which was converted to optically pure pramipexole by reacting (S)- 2,6-diamino-4,5,6,7-tetrahydro benzothiazole with propionic anhydride in THF and followed by reduction with borane THF complex . The reaction steps are shown in Scheme-2 as under:

SCHEME 2



The processes described above, suffer with the following drawbacks:

(i) Although, phthalamido protected 4-aminocyclohexanole gives better yield compared to monoprotected 4-aminocyclohexanol during oxidation and halogenation, the protection of 4-aminocyclohexanol with phthalic anhydride requires longer duration, approximately 36 hrs, hence will increase utility, manpower & overall cost of production. Furthermore, the efforts to repeat the reaction in the reported conditions were futile.

(ii) Bromination is carried out with hydrobromic acid in acetic acid, which is corrosive in nature. Work up of the reaction is very tedious. Moreover, diethyl ether has been used to remove the impurities. Diethyl ether is highly flammable and has low flash point, hence paused fire hazards at commercial scale.

(iii) Moreover, 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole requires laborious column chromatography to isolate and purify the 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole. Use of column chromatography is not feasible at commercial scale and gives low yield i.e. 50%.

(iv) Yet another disadvantage of the process lies in preparation and isolation of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole dihydrochloride as it also requires column chromatography and give very poor yield i.e. 26%.

Overall, the process disclosed in US 4886812, EP 186087 and EP 207696 for the preparation of pramipexole, are lengthy, low yielding, requires laborious column chromatography for several steps and use of corrosive and highly flammable materials. Therefore, there is a need to develop a process for preparing pramipexole and its pharmaceutically acceptable salts, solvates, which should be free from the above mentioned defects and should be simple, cost effective, high yielding and does not involve laborious column chromatography. Also, process should be devoid of highly flammable and corrosive material for commercial production.

OBJECTS OF THE INVENTION

Thus one object of the invention is to provide an improved process for the preparation of (S)-2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (II), which is a key intermediate for the synthesis of Pramipexole.

Another object of this invention is to provide an improved process for the preparation of pramipexole of formula (I) and its pharmaceutically acceptable salts, solvates if desired free from the above-mentioned defects.

Another object of this invention is to provide commercially viable process for the preparation of pramipexole and its pharmaceutically acceptable salts, solvates.

Yet another object of the process is to reduce the time of condensation of phthalic anhydride with 4-aminocyclohexanole.

Yet another object of the process is to simplify the work up of halogenation without using flammable solvent.

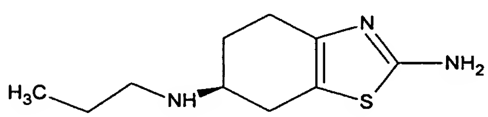
Yet another object of the invention is to provide a process for the preparation of Pramipexole, devoid of column chromatography at every stage of the process.

Further object of the invention is to overcome the problems associated with prior art process and to prepare Pramipexole by cost effective way.

In summary, the object of the present invention is to provide a simple, efficient, cost effective, devoid of corrosive, highly inflammable material, high yielding process for the preparation of Pramipexole of formula (I) and its pharmaceutically acceptable salts, solvates.

SUMMARY OF THE INVENTION

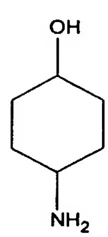
Thus according to one aspect of present invention, there is provided an improved process for the preparation of (S)- 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (II), an intermediate compound for formation of Pramipexole of Formula (I) and its pharmaceutically acceptable salts, solvates



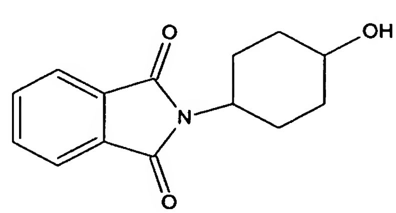
(I)

comprising the steps of

(a) reacting 4-amino cyclohexanol of formula (III) or its acid addition salts with phthalic anhydride in presence of acid catalyst and their salts, in polar aprotic solvent or its mixture with organic solvent, capable of removing water azeotropically to give 4-(phthalimido)-cyclohexanol of formula (IV)

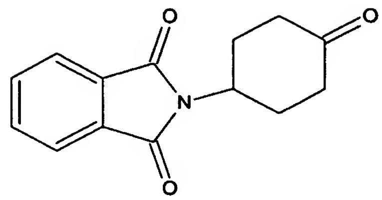


(III)



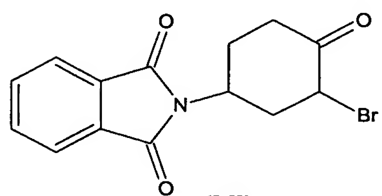
(IV)

(b) oxidizing 4-(phthalimido)-cyclohexanol of formula (IV) to give 4-(phthalimido)-cyclohexanone of formula (V)



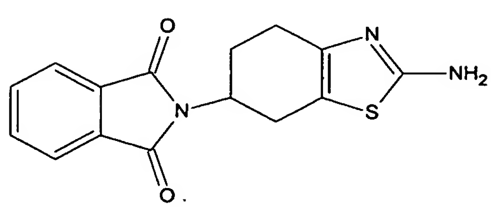
(V)

(c) brominating 4-(phthalimido)-cyclohexanone of formula (V) with brominating agent in organic solvent in presence of Lewis acid catalyst to prepare 2-bromo-4-(phthalimido)-cyclohexanone of formula (VI)



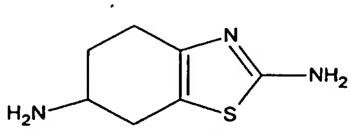
(VI)

(d) treating 2-bromo-4-(phthalimido)-cyclohexanone of formula (VI) with thiourea in organic solvent in presence of base to give 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazol of formula (VII)



(VII)

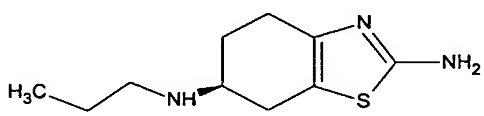
(e) reacting compound of formula (VII) with hydrazine hydrate and base in polar solvent to give racemic 2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (VIII)



(VIII)

(f) resolving racemic 2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (VIII) to prepare (6S)-2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (II)

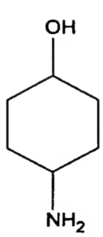
According to another aspect of present invention, there is provided an improved process for the preparation of Pramipexole of Formula (I) and its pharmaceutically acceptable salts/solvates



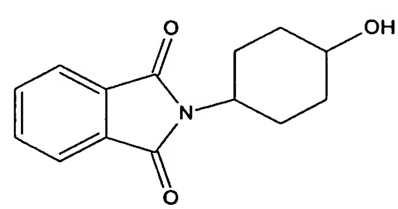
(I)

comprising the steps of

(a) reacting 4-amino cyclohexanol of formula (III) or its acid addition salts with phthalic anhydride in presence of acid catalyst and their salts, in polar aprotic solvent or its mixture with organic solvent, capable of removing water azeotropically to give 4-(phthalimido)-cyclohexanol of formula (IV)

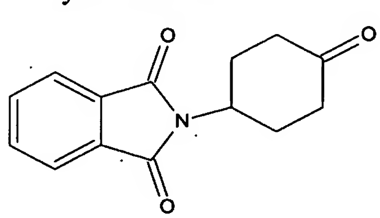


(III)



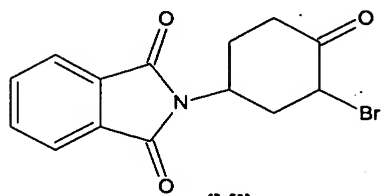
(IV)

(b) oxidizing 4-(phthalimido)-cyclohexanol of formula (IV) to give 4-(phthalimido)-cyclohexanone of formula (V)



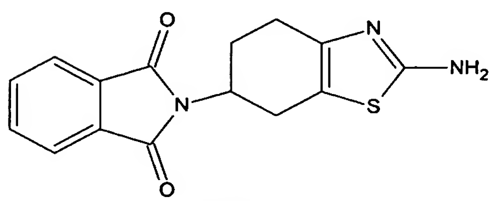
(V)

(c) brominating 4-(phthalimido)-cyclohexanone of formula (V) with brominating agent in organic solvent in presence of Lewis acid catalyst to prepare 2-bromo-4-(phthalimido)-cyclohexanone of formula (VI)



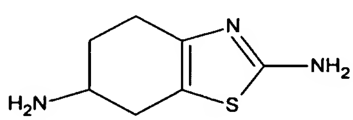
(VI)

(d) treating 2-bromo-4-(phthalimido)-cyclohexanone of formula (VI) with thiourea in organic solvent in presence of base to give 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazol of formula (VII)



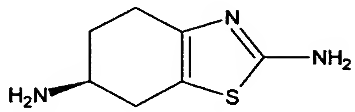
(VII)

(e) reacting compound of formula (VII) with hydrazine hydrate and base in polar solvent to give racemic 2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (VIII)



(VIII)

(f) resolving racemic 2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (VIII) to prepare (6S)-2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (II)



(II)

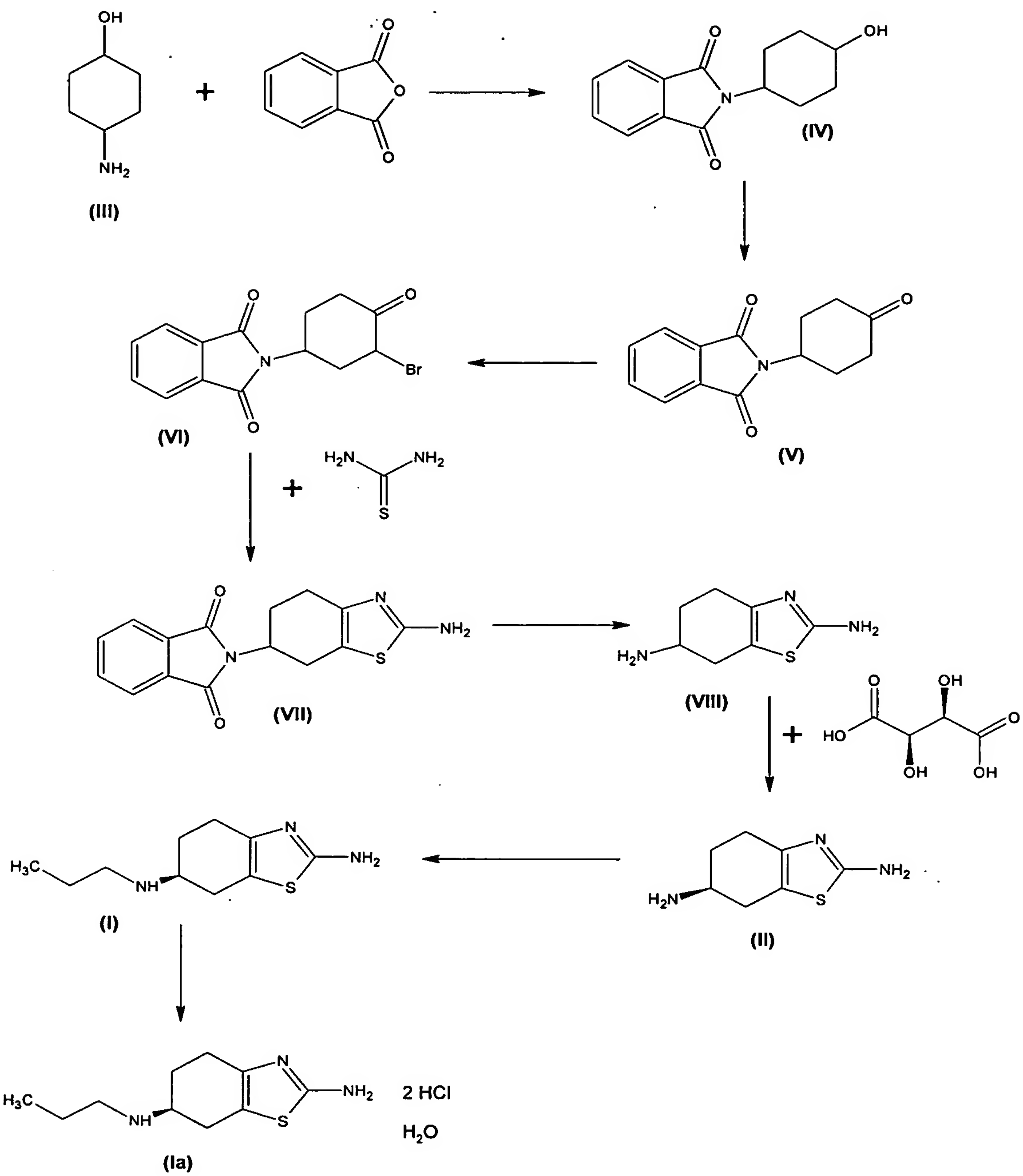
(g) coupling (6S)-2,6-dimino-4,5,6,7-tetrahydro-1,3-benzothiazole of formula (II) with propionaldehyde in presence of mineral acid in polar organic solvent and reducing agent to prepare (S)-(-)-2-Amino-6-(n-propylamino)-4,5,6,7-tetrahydrobenzothiazole of formula (I); and if desired

(h) converting (S)-(-)-2-Amino-6-(propylamino)-4,5,6,7-tetrahydrobenzothiazole to its pharmaceutically acceptable salts or solvates.

DETAILED DESCRIPTION OF THE INVENTION

According to an improved process for the preparation of Pramipexole of Formula (I) and its pharmaceutically acceptable salts, solvates when desired is shown in SCHEME-3 as follows:

SCHEME - 3



According to the present invention, 4-amino cyclohexanol of formula (III) is reacted with pthalic anhydride in presence of acid catalyst or their salts with organic bases, in polar aprotic solvent or its mixture with organic solvents, capable of removing water azeotropically.

Acid catalysts used in step (a) are sulphonic acid and their salts with organic bases and salt of inorganic acids with organic bases. It is selected form the group comprising of p-toluene sulphonic acid (PTSA), methane sulphonic acid, acid addition salts of pyridine, picoline, lutidine such as pyridine hydrochloride, pyridine hydrobromide, pyridine methane sulfonate, pyridine p-toluene sulphonate, picoline hydrochloride, picoline hydrobromide, picoline methane sulphonate, picoline p-toluene sulphonate, lutidine hydro chloride, lutidine hydrobromide, lutidine methane sulphonate, lutidine p-toluene sulphonate. The preferred acid catalyst is p-toluene sulphonic acid, pyridine p-toluene sulphonate

Polar aprotic solvent used in above step (a) is selected from group comprising of amide functional group such as dimethylformamide (DMF), dimethylacetamide (DMAC), N-methylpyrrolidinone (NMP), N-methylacetamide, N-methylformamide, , N,N-dimethylpropionamide, sulphoxide functional group such as dimethylsulfoxide, sulfolane, and ethers such as tetrahydrofuran (THF) and dioxane,

The preferred solvent is dimethyl formamide. Also, step (a) can be carried out in mixture of polar aprotic solvent with organic solvent, capable of removing water azeotropically such as toluene, cyclohexane and the like. The preferred organic solvent is selected from toluene, cyclohexane.

Reaction step (a) is carried out at 90°C to 140° C for 10 to 20 hrs and preferably for 12 to 18 hrs.

4-(phthalimido)-cyclohexanol of formula (IV) is further oxidized by conventional manner to give 4-(phthalimido)-cyclohexanone of formula (V). (4-phthalimido)-cyclohexanol is oxidized with potassium dichromate and H_2SO_4 to give 4-(phthalimido)-cyclohexanone.

4-(phthalimido)-cyclohexanone is further brominated with brominating agent in presence of Lewis acid as catalyst in organic solvent and converted to 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole with thiourea.

Brominating agent used in step (c) is bromine and a Lewis acid catalyst is selected from the group comprising of aluminium chloride, zinc chloride, stannous chloride.

Bromination can be carried out in both halogenated and non halogenated organic solvents. Most preferred halogenated solvent is selected from methylene dichloride, most preferred non halogenated solvents are alkyl acetate such as ethyl acetate , methyl acetate, propyl acetate and alcohols such as methanol, ethanol, and propanol. Step (c) is carried out at -5 to 40^{o} C and more preferably at 0°C to 10^{o} C.

2-bromo-4-(phthalimido)-cyclohexanone of formula (VI) is with or without isolating and is further treated with thiourea in presence of base in organic solvent to give 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole. Base used in step (d) is selected from alkaline earth metal carbonate , bicarbonates and acetate. Preferred base is selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, and sodium acetate and potassium acetate. The most preferred base used in step (d) is sodium bicarbonate or potassium bicarbonate.

Step (d) is carried out in organic solvent selected form alcohols, halogenated solvent or mixture there of. Alcohols is selected from methanol, ethanol, isopropanol, n-propanol, n-butanol or mixture there of. Halogenated solvent is selected form methylene dichloride, ethylene dichloride, chloroform.

2-amino-6-phthalimido-4,5,6,7-tetrahydrobenzothiazole of formula (VII) can also be prepared according to step (d) without isolating 2-bromo-4-(phthalimido)-cyclohexanone prepared in step (c). 2-bromo-4-(phthalimido)-cyclohexanone prepared by step (c) can be treated *in situ* with thoiurea in presence of base to give compound of formula (VII).

Reacting 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzothiazole of formula (VII) with hydrazine hydrate in presence of organic base in polar solvent to give racemic 2,6-diamino-4,5,6,7-tetrahydro benzothiazole (VIII). Moreover, 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (VIII) can also be isolated as its acid addition salts.

Organic base used in step (e) is selected from triethyl amine, pyridine, dimethyl aniline, lutidines, picolines and DBU. The preferred base used in step (e) is triethyl amine.

Polar solvent used in step (e) is selected form alcohols preferably methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol. The preferred solvent used in step (e) is ethanol or isopropanol.
Reaction step (e) is carried out at reflux temperature of above solvent

According to an important aspect of the invention, racemic 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole of formula (VIII) prepared in step (e) is without isolating, further converted to its desired isomer (S)- 2,6-diamino-4,5,67-tetrahydro-benzthiazole of formula (II)

Resolution of racemic 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (VIII) with L –tartaric acid lead to desired (S) isomer of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula II. Resolution of compound (VIII) comprises

(i) treating *in situ* or after isolating racemic 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (VIII), obtained in step (d) with (L) –tartric acid to give (S) tartrate salts of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole
(ii) isolating pure (S) tartrate salts of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole
(iii) converting pure (S) tartrate salts of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole to (S)-2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (II)

Reacting (S)- 2,6-diamino-4,5,6,7-tetrahydro benzothiazole of formula (II) with propionaldehde in suitable organic solvent in presence of mineral acid and reducing agent leads to formation of pramipexole of formula (I).

Mineral acid used in step (g) is selected from hydrochloric acid, sulfuric acid. Preferred mineral acid is sulfuric acid. Reducing agent used in step (g) is metal borohydride.

Preferred metal borohydride is selected from sodium borohydride, sodium cyanoborohydride. Preferred reducing agent is sodium borohydride

Organic solvent used in step (g) is polar organic solvent preferably alcohols selected from methanol, ethanol, isopropanol and n-propanol.

Step (g) is carried out at 0°C to 50° C. more preferably at 0°C to 30° C.

Pramipexole of formula (I) is further converted to its pharmaceutically acceptable salt / solvates by reacting with the respective acid in solvent selected from ethyl acetate, isopropyl acetate, methanol, ethanol or mixtures there of The preferred salt is Pramipexole dihydrochloride, which is available in the market, is prepared by reacting pramipexole with hydrochloric acid or HCl gas in solvent to give Pramipexole dihydrochloride. Also, its solvate, i.e. Pramipexole dihydrochloride monohydrate is prepared by addition of water during salt formation.

The process of the present invention leads to a significantly increase in yield at all the steps and does not involved column chromatography. Furthermore, the bromination and cyclization reaction steps have been carried out without using corrosive material. The reagent used in presence of catalyst provides a significant increase in yield from 50% to 90% without using column chromatography.

Thus the present invention provides an efficient process for the preparation of pramipexole of formula (I) and its pharmaceutically acceptable salts, solvates, which offers significant commercial advantages when preparing on an industrial scale. The present invention is having several advantages over known process.

The process of the present invention produces pramipexole of formula (I) and more particularly pramipexole dihydrochloride monohydrate is simple, environment friendly and economical and leads to an enhanced yield.

The current process further provides significant efficiencies at the commercial manufacturing. The overall cost and labor of the manufacturing process are reduced, as simpler machinery can be used, simple method is involved and fewer undesirable waste products are generated, all of which provides distinct commercial advantages for the preparation of Pramipexole on a commercial scale.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

EXAMPLES:

EXAMPLE-1:

Preparation of 4-(phthalimido)-cyclohexanol

(A) 300gms (2.608mole) of Trans-4-aminocyclohexanol was dissolve in 1500ml Dimethyl formamide and 1500ml of Toluene. Add 386gms(2.608mole) of Phthalic anhydride and 3gm(0.012mole) pyridinium p-toluene sulphonate. The reaction mixture is refluxed and remove water continuously from water separator, maintain this condition for 15-17 hrs. Evaporate solvent under reduced pressure. Add chloroform (3000ml). Wash organic part with 1000ml of 5%$NaHCO_3$, then wash with 1000ml of brine solution. After concentration of reaction mass, crystallize residue in Isopropyl alcohol.

YIELD : 503gms (79%)

PURITY : 99.66%

(B) 25gms(0.2123mole) Trans-4-aminocyclohexanol was dissolve in 100ml cyclohexane and 100ml DMF. Add 128.6gm(0.8689mole) phthalic anhydride and 0.25gm(0.001mole) pyridinium p-toluene sulphonate. Reflux mass at 90-95°C for 19 hrs. Remove continuously water from water separator. Cool mass to 40°C, remove solvent under reduced pressure. Dissolve mass in 250ml chloroform, washed chloroform layer with 5%$NaHCO_3$ solution and brine solution. Evaporate chloroform and residue was crystallizing in isopropyl alcohol.

YIELD: 38gms(71%)

(C) 25gms (0.2123mole) Trans-4-aminocyclohexanol was dissolved in 125ml of toluene and 125ml of DMF. Add 32.17gm(0.2123mole) phthalic anhydride and 0.25gm (0.0066 mole) of p-toluene sulphonic acid. Reflux mass at 130°-135°C for 10hrs. Remove continuously water from water separator. Cool mass to 40^{0}C.remove solvent under reduced pressure. Dissolve mass in 250ml chloroform, washed chloroform layer with 5%NaHCO3 solution and brine solution. Evaporate chloroform and residue was crystallizing in isopropyl alcohol.

YIELD: 41gms(77%)

(D) 25gms(0.2123mole) Trans-4-aminocyclohexanol was dissolve in 125ml of toluene and 125ml of DMF. Add 32.17gm(0.2123mole) phthalic anhydride and 0.25gm(0.0074 mole) of pyridine hydrobromide. Reflux mass at 130°-135°C for 15-17 hrs. Remove continuously water from water separator. Cool mass to 40^{0}C.remove solvent under reduced pressure. Dissolve mass in 250ml chloroform, washed chloroform layer with 5%$NaHCO_3$ solution and brine solution. Evaporate chloroform and residue was crystallizing in isopropyl alcohol.

YIELD: 37gms(69.4%)

EXAMPLE: 2

Preparation of 4-(phthalimido)- cyclohexanone

190gms(0.7755mole) 4-phthalimido cyclohexanol are dissolve in 1480ml chloroform. Add solution of H_2SO_4 (435.87gm, 4.4476mole conc. H_2SO_4 was added in 900 ml water). Cool mass to 25°C,add lot wise 180.5gm(0.6139mole) potassium dichromate in one hour. Stir mass for three hours, add 900 ml water and separate organic phase. Organic phase was washed with water and 2% NaHCO3 solution, after drying and concentration of extracts product was isolated by adding methanol and water mixture.

YIELD: 175g(92.4%)

PURITY: 96.01%.

EXAMPLE: 3

Preparation of 3-bromo-4-(phthalimido)- cyclohexanone

(A) 15gm (0.0617mole) 4-phthalimido cyclohexanone was dissolve in 150ml methanol. Heat the mass to 40^0C. Add Br_2 solution (9.8gm Br_2 in 25ml of methanol) and 0.25gm of $AlCl_3$ under stirring. Stop stirring and allow initiating bromination and finding clear solution then add remaining quantity of Br_2 solution and stir for 10-15mins. Add 10ml water and stir for 10mins more. Then filter the white solids obtain .Dry it at 50^0C for 2-3hrs.

YIELD: 12.5gm(62.8%)

(B) 15gm (0.0617mole) 4-phthalimido cyclohexanone was dissolve in 150ml Ethyl acetate. Cool the mass to 0^0C. Add Br_2 solution (9.8gm Br_2 in 25ml of methanol) and 0.25gm of $AlCl_3$ under stirring. Stop stirring and allow initiating bromination and finding clear solution then add remaining quantity of Br_2 solution and stir for 10-15mins. Wash the reaction mass with 75ml 2% NaS_2O_3 solution then wash organic phase with 75ml 8%$NaHCO_3$. Then in last wash it with brine solution. Collect organic masses and evaporate it under vacuum. Dry it at 50^0C for 2-3hrs.

YIELD: 15gms(75.2%)

EXAMPLE-4:

Preparation of 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole

100gm(0.4115mole) 4-phthalimido cyclohexanone was dissolve in 1000ml dichloromethane. Cool the mass to 0^0C. Add 25ml Br_2 solution (65.8gm Br_2 in 100ml of dichloromethane) and 0.3gm anhydrous $AlCl_3$ under stirring. Stop stirring and allow initiating bromination and finding clear solution then add remaining quantity of Br_2 solution and stirr for 10-15 min. Wash the reaction mass with 250ml 2% NaS_2O_3 solution then wash organic phase with 250ml 8%$NaHCO_3$. Collect organic phase and add 46gm (0.6052mole) thiourea, 34gm (0.4047mol) $NaHCO_3$ and 350ml methanol. Reflux reaction mass for 2-3 hrs. Distill off dichloromethane and methanol. Add 690ml DM water in residue. Filter the product and purified wet product by hot methanol.

YIELD: 110gm(89%)

PURITY: 96.45%

EXAMPLE-5:

Preparation of Racemic 2,6-diamino-4,5,6,7-tetrahydro benzothiazole

100gm(0.3344mole) 2-amino-6-phthalimido-4,5,6,7-tetrahydro benzothiazole was suspended in 500ml isopropyl alcohol. Add 20.05gm(0.4010mole) hydrazine hydrate and 7.26gm (0.0718mole) Triethylamine. Reflux for 2-3hrs. Cool the mass to 10^0 C , Filter the slurry and wash with chilled isopropyl alcohol. Isolated mixture of compounds are recrystalize in absolute alcohol

YIELD: 50gm(88.46%)

EXAMPLE –6:

Preparation of (S)- Tartarate salt of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole

100gm (0.5917mol) of 4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine was added in 1000ml DM water. Heat it to 70^0C and add 88.75gm (0.5917mole) L(+)-Tartaric acid. Stirr for 1.5hr, cool to 60^0C. Filter hot. Stir the filtrate for 10-12hrs, cool to 5^0C. Stir for 30mins. Filter and recrystallize by water.

PURITY : 99.5% (chiral purity)

EXAMPLE-7:

Preparation of (S)-2,6-diamino-4,5,6,7-tetrahydro benzothiazole

100gm(0.3134mole) (S)-Tartarate salt of 2,6-diamino-4,5,6,7-tetrahydro benzothiazole was added to 79.69ml water. Cool the reaction mass to 0-5^0C with stirring. Add 71.99ml conc. HCl slowly and drop wise. Then add 240ml 85% KOH solution drop wise to reaction mass. Maintain temperature 0-5^0C during complete addition. Stir reaction mass for 1-2hrs at 0-5^0C. Filter the product.

YIELD : 56gm(1.05%)

PURITY : 99.6%.

EXAMPLE-8:

Preparation of (S)-(-)-2-Amino-6-(n-propylamino)-4,5,6,7-tetrahydrobenzothiazole or Pramipexole of formula (I)

50gm (0.2958mole) (6S)-4,5,6,7-tetrahydro-1,3-benzthiazole-2,6-diamine was dissolved in 1500ml methanol. Bring down temp of solution to 0^0C. Add 20.68gm(0.3566mole)

propionaldehyde and 1.3gm conc. sulfuric acid (0.044mole) . After stirring to 90 minutes add 16.78gm (0.4435mole) sodium borohydride. Allow increasing temperature of mass to 25^{0}C. After one hrs add second lot of 17.22gm (0.2970mole) propionaldehyde and agitate for 10-15mins. Then add 11.19gm (0.2957mole) sodium borohydride and stirr for 40mins. Add 150-ml brine solution and stirr for 30mins. Distill off solvent under reduced pressure at 40^{0}C.. Add 500ml ethyl acetate and water, Separate organic phase, dry it and distilled off ethyl acetate under reduced pressure at 40^{0}C. Residue is crystallizing in Acetonitrile.

YIELD: 34.75 gm (80.1%)

PURITY: 99.5%

^{1}H NMR in DMSO: 1.14 ppm (d, 3H) C(3'); 4.12 ppm (m,1H) C(2'); 3.0 ppm (m,1H) C(1') ; 3.54 ppm (m,1H) C(6) ; 3.10 ppm (m,2H) C(7) ; 2.34 ppm (m, 2H) C(3); 2.09 ppm (m,2H) C(4)

^{13}C NMR in DMSO: C(4) 23.2 ppm , C(5) 20.9 ppm , C(7) 24.69 ppm , C(6) 52.65 ppm , C(1') 51.51, C(2') 62.30, C(3') 21.02 ppm ; thiazole ring C(2') 168.7 ppm ; C(4') 132.8 ppm, C(5') 110.83 ppm

EXAMPLE-9

Preparation of Pramipexole dihydrochloride monohydrate

100gm (0.4739mole) (S)-Pramipexole was dissolve in 800ml ethanol. Heat it to 50-55^{0}C. Add 10gm-charcoal powder and stirr for 15-20 min. Filter through hyflow and wash it with 200ml ethanol. Add 8.53gm (0.4739mole) water cool the reaction mass to 0-5^{0}C. Pass dry HCl gas to reaction mass till pH becomes 2. Stir for 7-8hrs. Filter the product. Purified by refluxing with ethanol.

YIELD : 127gm(88.7%)

PURITY : 99.8%

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.